REMARKS

I. Claim Status

Applicants hereby amend claims 1 and 20, and cancel claims 7-12, 22, and 42-47. Claim 1 is amended to comply with the Office's reinterpretation of the Restriction Requirement of April 10, 2006.[1] Claims 1 and 20 are also amended for stylistic reasons and to recite that globotriaosylceramide is reduced. Support for the claim amendments is present in the specification and originally-filed claims at, e.g., original claims 1 and 7-9. No new matter is added. Applicants respectfully request entry, consideration and examination of this response and the timely allowance of claims 1, 3-4, 6, 14-18, 20, 37, and 40-41, which are pending and under examination, in view of the arguments set forth below.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

The Office has rejected claims 1, 3, 4, 6, 7, 9, 14-18, 20, 36, 37, 40 and 41 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Office Action at 3. The Office alleges that "the specification, while being enabling for reducing globotriaosylceramide (GB3)[2] in a patient with Fabry disease by infusing an AAV vector expressing alpha-galactosidase A protein under the control of liver-specific promoter in combination with

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[1] Applicants elected Group I, "drawn to a method of treating a subject having a lysosomal disease, such as Fabry disease, comprising administering a gene therapy vector and an exogenously produced natural or recombinant lysosomal hydrolase, such as alpha-galactosidase" in response to the Restriction Requirement of April 10, 2006. The Office has been examining claims drawn to lysosomal storage diseases since Applicants' election. However, the Office now asserts that it considers "a lysosomal storage disease, such as Fabry disease" to mean Fabry disease alone. Office Action at 2. Thus, the Office asserts that "claims 42-46 will NOT be considered at this time." *Id.* Although Applicants disagree with the Office's reinterpretation of its original Restriction Requirement, Applicants have amended claim 1 and cancelled claims 22 and 42-46 solely in order to expedite prosecution.

[2] The Examiner abbreviates globotriaosylceramide in the Office Action as Gb3, GB3, and GL-3. *See, e.g.,* Office Action at 3, 5, 8. Globotriaosylceramide is abbreviated in the specification as GL-3 and GL3. *See* Specification at [0103].

infusing a recombinant alpha-galactosidase A protein to said patient, does not reasonably provide enablement for treating a subject having Fabry disease by first administering a gene therapy vector expressing alpha-galactosidase A protein under the control of a liver-specific regulatory element and then administering natural or recombinant alpha-galactosidase A protein so as to provide therapeutic effect for treating Fabry disease in vivo and the pathological symptoms of Fabry disease have been ameliorated or eliminated." *Id.*

Without acquiescing in the Examiner's rejection, Applicants note that the amended claims are directed to methods of reducing globotriaosylceramide in a subject having Fabry disease, i.e., to subject matter that the Office has admitted to be enabled. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

III. Rejections Under 35 U.S.C. § 103

The Office has rejected claims 1, 3, 7-9, 14-18, 20, 38, 40 and 41 under 35 U.S.C. § 103(a) as being unpatentable over Schiffmann et al., *Proc. Natl. Acad. Sci. USA* 97:365-370 (2000) ("*Schiffmann*") and Ziegler et al., *Hum. Gene There.* 10:1667-1682 (1999)("*Ziegler*") in view of U.S. Patent No. 7,090,836 to Desmaris et al. ("*Desmaris*") and U.S. Patent No. 7,312,324 to Souza et al. ("*Souza*"). Applicants respectfully traverse.

To determine whether a claimed invention is obvious under 35 U.S.C. § 103, the Office must apply the *Graham* test, which requires the Office: (1) to determine the scope and content of the prior art; (2) to identify any differences between the prior art and the claims at issue; (3) to determine the level of ordinary skill in the applicable art; and (4) to evaluate evidence of secondary considerations. *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); *see also KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007); M.P.E.P. § 2141. The obviousness or nonobviousness of the claimed invention must then be evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18.

The Office has relied on *Schiffmann* for its teaching of enzyme replacement therapy in Fabry disease, and on *Ziegler* for its teaching of gene therapy in Fabry disease. The Office has relied upon *Desmaris* as providing the rationale to combine enzyme replacement therapy with small molecule therapy for the treatment of Fabry disease. It has further relied upon *Souza* for its teaching of "combining promoter elements that have the potential to direct effective and sustained expression with liver specific enhancer elements." Office Action at 13.

As noted above, the Office alleges that *Desmaris* provides the rationale to combine enzyme replacement therapy with small molecule therapy for the treatment of Fabry disease. Specifically, the Office alleges that "Desmaris teaches combining gene therapy in treating MPS I, which is also a lysosomal storage disease." Office Action at 13. However, the Office's characterization ignores the specific teachings of *Desmaris*.

Desmaris teaches the administration of gene therapy vectors into the brain "to facilitate expression of the lysosomal enzyme in the brain . . . [so as to] provide[] treatment for the neurological aspects of these diseases." *Desmaris* at Abstract. Because the gene therapy is limited to the brain, *Desmaris* teaches that "gene therapy trial targeted to the brain in this disease will have to be combined with enzyme replacement in the periphery." *Desmaris* at col. 5, ll. 51-53. In essence, *Desmaris* teaches two concurrent monotherapies for treating two different parts of the body. Thus, the rationale of *Desmaris* is not applicable to the combination of *Schiffmann* and *Ziegler*, because neither contemplates the use of brain-specific gene therapy.

Further, *Desmaris* is explicitly inapplicable to Fabry disease. *Desmaris* addresses "a need in the art for a treatment of the central nervous system pathology in lysosomal storage diseases in which neurological symptoms are either predominant, as in MPS III and MLD, or highly determinant for the clinical prognosis, as in MPS I." *Desmaris* at col. 1, ll. 41-46. For *Desmaris*, Fabry disease is not a disease in which neurological symptoms are significant. Rather, *Desmaris* characterizes Fabry as a "disease[] that do[es] not affect the brain." *Id.* at col. 4, ll. 36-37. Accordingly, *Desmaris*

specifically teaches away from combination with *Schiffmann* and *Ziegler*, both singly and in combination. For that additional reason, *Desmaris* fails to provide a rationale for combining *Schiffmann* and *Ziegler*.

As rationale for introducing *Souza*, the Office alleges that "it was known the primary target tissue in treating Fabry disease is liver." Office Action at 14. The Office has not provided any basis or reference for that statement. As the M.P.E.P. explains, "[i]t would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known." M.P.E.P. § 2144.03(A) (emphasis in original). Moreover, "[i]t is *never* appropriate to rely solely on 'common knowledge' in the art without evidentiary support in the record, as the principal evidence upon which a rejection is based." *Id.* (emphasis added). For at least that reason, the Office has failed to provide a rationale to combine *Souza* with *Schiffman*, *Ziegler*, and *Desmaris*, individually or in combination.

The Office's assertion is not only unsupported, but appears to be factually incorrect. For example, Desnick et al., *Ann. Intern. Med.* 138:338-346 (2003)("*Desnick*")[3] teaches that "[t]he major debilitating manifestations of Fabry disease result from the progressive accumulation of globotriaosylceramide in the vascular endothelium . . . , leading to ischemia and infarction, especially in the kidney, heart, and brain." *Desnick* at 339. Similarly, Eng et al., *N. Engl. J. Med.* 345:9-16 (2001)("*Eng*")[4] teaches that "progressive accumulation of globotriaosylceramide and related glycosphingolipids in vascular endothelial lysosomes of the kidneys, heart, skin, and brain leads to the main disease manifestations." *Eng* at 9. Further,"[i]n classically affected males, the progressive glycosphingolipid accumulation, particularly in the vascular endothelium . . . , leads to renal, cardiac, and cerebrascular manifestations and early death." *Desnick* at 338. For that additional reason, the Office has failed to provide

[3] This document was submitted in an Information Disclosure Statement (IDS) initialed by the Examiner on May 21, 2007.
[4] This document was submitted in an IDS initialed by the Examiner on May 21, 2007.

a rationale to combine *Souza* with *Schiffman*, *Ziegler*, and *Desmaris*, individually or in combination.

Finally, liver-specific expression, as taught by *Souza*, would vitiate *Desmaris*' invention of "a treatment of the central nervous system pathology" by means of a "nucleic acid molecule [that] comprises at least . . . a promoter highly active in the brain." *Demaris* at col. 1, ll. 42-43, col. 2, ll. 22-23. By definition, liver-specific regulatory elements will not result in high levels of expression in the brain. *Souza* thus teaches away from the combination with *Desmaris*. For that further reason, the Office has failed to provide a rationale for combining *Schiffmann*, *Ziegler*, *Desmaris*, and *Souza*.

For all of the reasons above, the Office has failed to provide any convincing reason why one of skill of art would be motivated to combine enzyme replacement therapy and gene therapy with a liver-specific regulatory element for the reduction of globotriaosylceramide in subjects having Fabry disease. That is to say, the Office has not "explain[ed] why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art." M.P.E.P. § 2141 (III). Accordingly, the Office has failed to establish a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this Application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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